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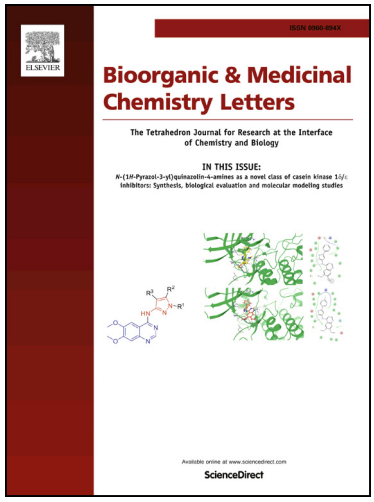

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Synthesis of some monosaccharide-related ester derivatives as insecticidal and acaricidal agents

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Abstract:

To develop natural-product-based pesticidal agents, a series of monosaccharide-related ester derivatives (**17a-q** and **18a-f**), glucose (xylose)-piperic acid/piperic acid-like conjugates, were synthesized. Three-dimensional structures of compounds **17b**, **17g**, **17h**, and **17n** were unambiguously determined by single-crystal X-ray diffraction. Especially compounds **18e** and **18f** exhibited the most potent insecticidal and acaricidal activities against *Mythimna separata* and *Tetranychus cinnabarinus*. Their structure-activity relationships were also discussed.

Keywords: Ester; Monosaccharide; Piperine; Insecticidal activity; Acaricidal activity

Oriental armyworm (*Mythimna separata* Walker) and spider mite (*Tetranychus cinnabarinus* Boisduval) are two crop-threatening insect pests, and their outbreaks are generally hard to control.[1-3] Meanwhile, due to extensive and unreasonable application of synthetic agrochemicals, development of resistance in pest populations and negative impacts on human health and environment has occurred.[4,5] Consequently, development of the potential alternatives to efficiently control insect pests is highly desirable.[6-8]

Piperine (Figure 1), a simple alkaloid isolated as from *Piper nigrum* Linn., exhibited a variety of biological properties including anti-inflammatory activity, antimicrobial activity, antitumor activity, and insecticidal activity.[9] Previously, by using piperine as a lead compound, we prepared a series of piperine-based hydrazone derivatives (**I**, Figure 1),[10] and piperine-based phenylsulfonylhydrazone derivatives (**II**, Figure 1)[11] as insecticidal agents; especially piperine-based 4-ethylphenylsulfonylhydrazone and piperine-based 4-bromophenylsulfonylhydrazone exhibited more potent narcotic activity against *M. separata* than wilfortrine and wilforgine, two macrocyclic alkaloids isolated from *Tripterygium hypoglaucum* Hutch.[11] On the other hand, Xu et al. pioneeringly reported some glucose-fipronil conjugates (**III** and **IV**, Figure 1) showing excellent phloem mobility.[12-16] Huang et al. found that some fluorine-containing saccharide esters (**V** and **VI**, Figure 1) showed potent antiviral activities against tobacco mosaic virus.[17] In continuation of our program aimed at the development of natural-product-based pesticidal agents,[18-20] therefore, in this Letters some glucose

(xylose)-piperic acid conjugates (**VII**, Figure 1) were prepared by combination of glucosides with the piperic acid together. Meanwhile, to study the structure-activity relationships of these type compounds, other glucose (xylose)-piperic acid-like conjugates (**VIII** and **IX**, Figure 1) were also synthesized. Their insecticidal and acaricidal activities were evaluated against *Mythimna separata* and *Tetranychus cinnabarinus*.

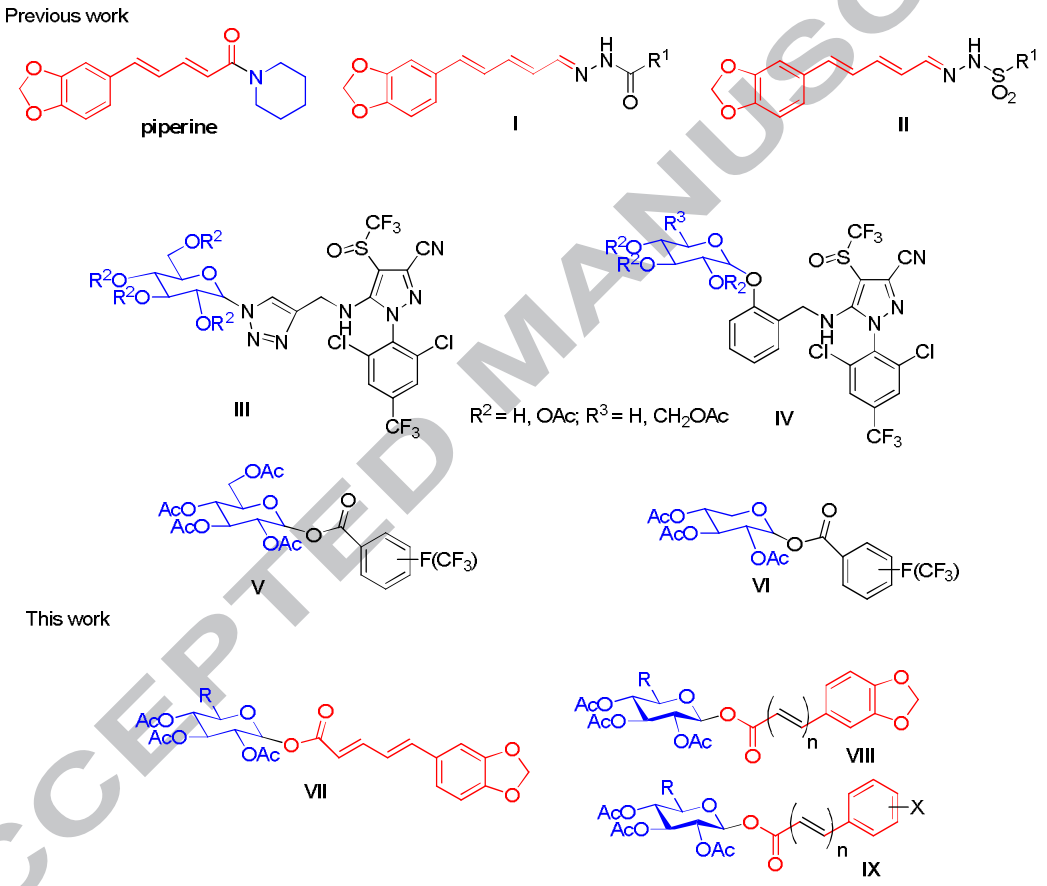
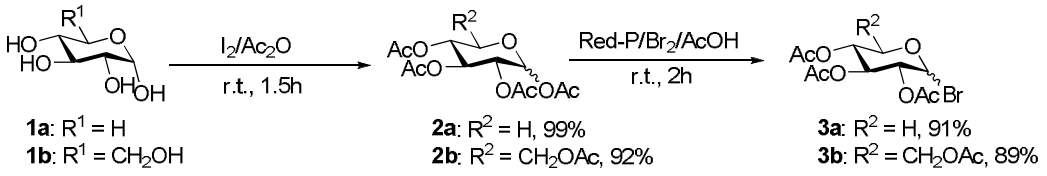
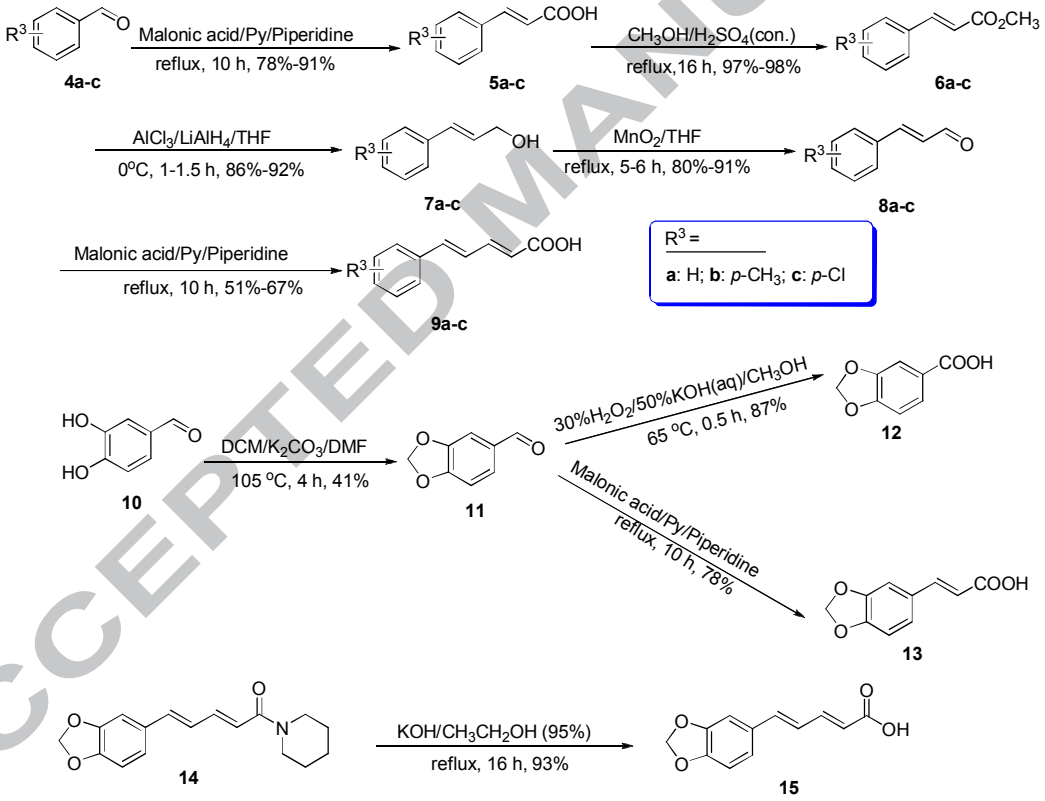


Figure 1. The chemical structures of piperine, its derivatives (**I** and **II**), monosaccharide-related derivatives (**III**- **VI**), and target compounds **VII-IX**.



Scheme 1. Synthesis of 2,3,4-tri-*O*-acetyl-*β*-*D*-xylopyranosylbromine (**3a**) and 2,3,4,6-tetra-*O*-acetyl-*β*-*D*-glucopyranosylbromine (**3b**).

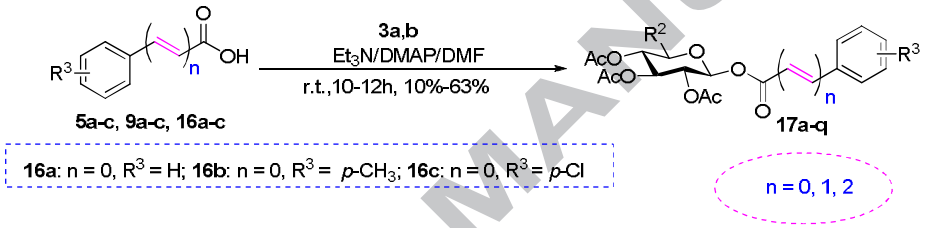
As shown in Scheme 1, 1,2,3,4-tetra-*O*-acetylxylose (**2a**) and 1,2,3,4,6-penta-*O*-acetylglucose (**2b**) were firstly prepared by reaction of iodine with xylose (**1a**) and glucose (**1b**), respectively.[21] Then two intermediates, 2,3,4-tri-*O*-acetyl-*β*-*D*-xylopyranosylbromine (**3a**) and 2,3,4,6-tetra-*O*-acetyl-*β*-*D*-glucopyranosylbromine (**3b**), were smoothly obtained by reaction of bromine with **2a** and **2b**, respectively.[22]



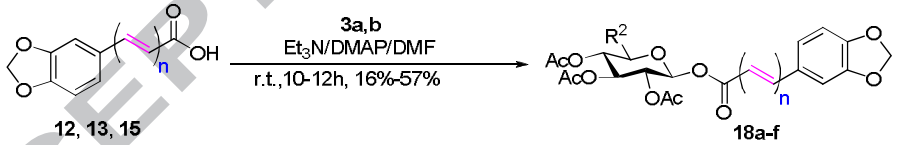
Scheme 2. Synthesis of different aromatic carboxylic acids (**5a-c**, **9a-c**, **12**, **13**, and **15**).

As described in Scheme 2, malonic acid reacted with benzaldehydes (**4a-c**) to give cinnamic acids (**5a-c**);[23] methyl cinnamates (**6a-c**) were prepared by reaction of

5a-c with methanol in the presence of conc. sulfuric acid.[10] Then reduction of **6a-c** with $LiAlH_4$ and $AlCl_3$ afforded γ-phenylallyl alcohols (**7a-c**), which were oxidized by MnO_2 to produce phenylacrolein (**8a-c**).[10] Finally, 5-phenyl-2,4-pentadienoic acids (**9a-c**) were obtained by reaction of **8a-c** with malonic acid.[23] 3,4-Methylenedioxybenzoic acid (**12**) and 3,4-methylenedioxycinnamic acid (**13**) were obtained from 3,4-methylenedioxybenzaldehyde (**11**),[24] which was prepared from 3,4-dihydroxybenzaldehyde (**10**).[25] The piperic acid (**15**) was obtained from piperine (**14**) by the basic hydrolysis.[26]



17a: n = 0, R^2 = CH_2OAc, R^3 = H; **17b**: n = 1, R^2 = CH_2OAc, R^3 = H; **17c**: n = 2, R^2 = CH_2OAc, R^3 = H;
17d: n = 0, R^2 = CH_2OAc, R^3 = *p*-CH_3; **17e**: n = 1, R^2 = CH_2OAc, R^3 = *p*-CH_3; **17f**: n = 2, R^2 = CH_2OAc, R^3 = *p*-CH_3;
17g: n = 0, R^2 = CH_2OAc, R^3 = *p*-Cl;**17h**: n = 1, R^2 = CH_2OAc, R^3 = *p*-Cl; **17i**: n = 2, R^2 = CH_2OAc, R^3 = *p*-Cl;
17 j: n = 0, R^2 = H, R^3 = H;**17k**: n = 1, R^2 = H, R^3 = H; **17l**: n = 2, R^2 = H, R^3 = H;
17m: n = 0, R^2 = H, R^3 = *p*-CH_3; **17n**: n = 1, R^2 = H, R^3 = *p*-CH_3; **17o**: n = 2, R^2 = H, R^3 = *p*-CH_3;
17p: n = 0, R^2 = H, R^3 = *p*-Cl; **17q**: n = 1, R^2 = H, R^3 = *p*-Cl.



Scheme 3. Synthesis of 2,3,4-tri-*O*-acetyl-*β*-*D*-xylopyranosylcarbonyl/ 2,3,4,6-tetra-*O*-acetyl-*β*-*D*-glucopyranosylcarbonyl derivatives (**17a-q** and **18a-f**).

As shown in Scheme 3, target compounds **17a-q**, and **18a-f** were obtained by reaction of 2,3,4-tri-*O*-acetyl-*β*-*D*-xylopyranosylbromine (**3a**)/2,3,4,6-tetra-*O*-acetyl-*β*-*D*-glucopyranosylbromine (**3b**) with the corresponding

carboxylic acids (**5a-c**, **9a-c**, **12**, **13**, **15**, and **16a-c**). Their structures were well characterized by ^{1}H NMR, optical rotation, HRMS and mp (see Supplementary data).

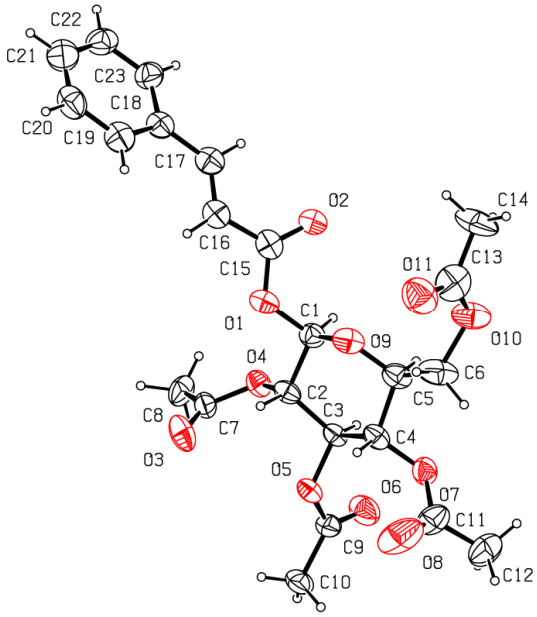


Figure 2. X-ray crystal structure of compound **17b**.

The represental three-dimensional structure of **17b** was shown in Figure 2, and other X-ray crystal structures of compounds **17g**, **17h**, and **17n** were depicted in Figures S1-S3 (see Supplementary data). The substituents on the C=C double bond of **17b**, **17h**, and **17n** all adopted *E* configuration. Crystallographic data (excluding structure factors) for the structures of **17b**, **17g**, **17h**, and **17n** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1552146, 1552149, 1552147, and 1552150, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

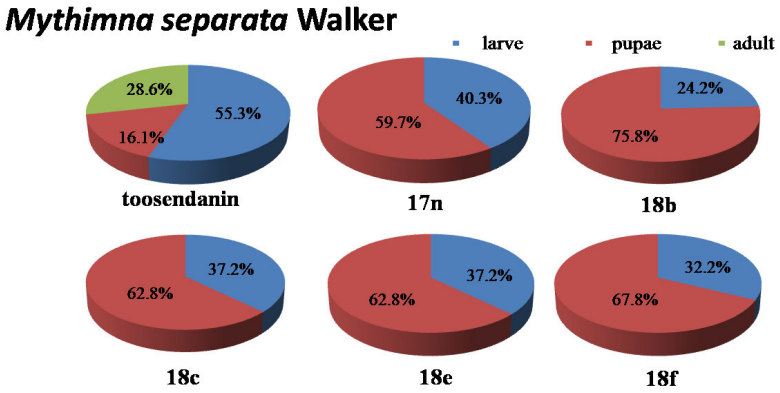


Figure 3. The percentages of the final mortality rates of *Mythimna separata* at different growth stages of compounds **17n**, **18b**, **18c**, **18e**, **18f** and toosendanin.

The insecticidal activity of compounds **17a-q** and **18a-f** against the pre-third-instar larvae of *Mythimna separata* was evaluated by leaf-dipping method at a concentration of 1 mg/mL.[27-29] Toosendanin, a commercial botanical insecticide isolated from *Melia azedarach*, was used as a positive control at 1 mg/mL. Leaves treated with acetone alone were used as a blank control group. The symptoms of *M. separata* treated with the above compounds only during larval and pupation stages were in the same way as in our previous reports.[27-29] For example, some larvae with the wrinkled bodies died at the larval stage (Figure S4, see Supplementary data), and some larvae molted to malformed pupae or died during the pupation period (Figure S5, see Supplementary data). Interestingly, in this experiment malformed moth did not appear during the adult emergence stage. Finally, the percentages of the final mortality rates (FMRs) at different growth stages of **17n**, **18b**, **18c**, **18e**, **18f** and toosendanin were described in Figure 3. The percentages of FMRs at larval, pupation, and adult emergence stages of

toosendanin were 53.3%, 16.1% and 28.6%, respectively. On the contrary, the percentages of FMRs of **17n**, **18b**, **18c**, **18e**, and **18f** were only at larval and pupation stages. Especially more than half of FMRs for compounds **17n**, **18b**, **18c**, **18e**, and **18f** were at the pupation stage. As shown in Table 1, among all derivatives, only 2,3,4-tri-*O*-acetyl-*β*-*D*-xylopyranosylcarbonyl derivative **18f** showed higher insecticidal activity than piperine and toosendanin; for instance, FMRs of **18f**, piperine and toosendanin were 51.7%, 44.8%, and 48.3%, respectively. Generally, the insecticidal activity of **18a-f** was more potent than that of **17a-q**, and it suggested that the 3,4-methylenedioxy of **18a-f** was necessary for the activity. The insecticidal activity of 2,3,4-tri-*O*-acetyl-*β*-*D*-xylopyranosylcarbonyl derivatives **18d-f** was more potent than that of 2,3,4,6-tetra-*O*-acetyl-*β*-*D*-glucopyranosylcarbonyl derivatives **18a-c**. Among derivatives **18a-f**, it demonstrated that introduction of one C=C double bond or two C=C double bonds on **18a** or **18d** was important for the insecticidal activity (e.g., **18a** vs. **18b** vs. **18c**; **18d** vs. **18e** vs. **18f**).

Table 1

Insecticidal activity of compounds **17a-q** and **18a-f** against *M. separata* on leaves treated at a concentration of 1 mg/mL.

Compound	Corrected mortality rate (mean ± SD, %) [a]		
	10 days	25 days	36 days
17a	6.7 ± 3.3	17.2 ± 5.8	24.1 ± 8.8
17b	10.0 ± 5.8	31.0 ± 3.3	34.5 ± 3.3
17c	6.7 ± 3.3	27.6 ± 5.8	31.0 ± 8.8
17d	13.3 ± 3.3	34.5 ± 3.3	34.5 ± 3.3
17e	16.7 ± 3.3	31.0 ± 3.3	37.9 ± 5.8
17f	10.0 ± 5.8	34.5 ± 6.7	34.5 ± 6.7
17g	6.7 ± 3.3	24.1 ± 3.3	24.1 ± 3.3
17h	6.7 ± 3.3	20.7 ± 3.3	24.1 ± 6.7

17i	3.3 ± 3.3	24.1 ± 6.7	27.6 ± 5.8
17j	13.3 ± 3.3	27.6 ± 0	31.0 ± 3.3
17k	13.3 ± 3.3	31.0 ± 3.3	34.5 ± 3.3
17l	10.0 ± 0	31.0 ± 3.3	34.5 ± 6.7
17m	16.7 ± 8.8	37.9 ± 0	37.9 ± 0
17n	16.7 ± 3.3	34.5 ± 3.3	41.4 ± 3.3
17o	13.3 ± 8.8	37.9 ± 5.8	37.9 ± 5.8
17p	13.3 ± 3.3	31.0 ± 3.3	34.5 ± 6.7
17q	6.7 ± 3.3	24.1 ± 3.3	27.6 ± 5.8
18a	6.7 ± 3.3	31.0 ± 3.3	34.5 ± 3.3
18b	10.0 ± 0	34.5 ± 3.3	41.4 ± 3.3
18c	16.7 ± 3.3	41.4 ± 3.3	44.8 ± 3.3
18d	13.3 ± 6.7	34.5 ± 6.7	37.9 ± 5.8
18e	16.7 ± 3.3	41.4 ± 6.7	44.8 ± 3.3
18f	16.7 ± 3.3	44.8 ± 3.3	51.7 ± 3.3
piperine (**14**)	20.0 ± 0	37.9 ± 5.8	44.8 ± 3.3
toosendanin	16.7 ± 3.3	34.5 ± 3.3	48.3 ± 0

[a]Values are the mean ± SD of three replicates.

Table 2

Acaricidal activity of compounds **1a**, **1b**, **2a**, **2b**, **17a-q** and **18a-f** against the female adults of *Tetranychus cinnabarinus* at a concentration of 1 mg/mL.

Compound	Corrected mortality rate (mean ± SD, %) [a]		
	24 hours	48 hours	72 hours
1a	0 ± 0	2.1 ± 2.1	1.0 ± 1.8
1b	1.1 ± 1.1	1.1 ± 1.1	2.3 ± 2.2
2a	2.6 ± 1.3	2.7 ± 0.1	2.9 ± 1.3
2b	2.4 ± 2.4	2.6 ± 2.1	4.1 ± 1.2
17a	3.4 ± 0.7	4.2 ± 0.6	25.9 ± 3.6
17b	1.6 ± 0.6	6.2 ± 1.1	43.8 ± 3.0
17c	2.2 ± 0.7	8.1 ± 0.5	23.2 ± 2.8
17d	2.3 ± 0.9	6.7 ± 1.3	32.3 ± 4.1
17e	1.7 ± 0.5	8.9 ± 1.2	34.6 ± 5.4
17f	2.6 ± 0.9	6.5 ± 0.9	24.9 ± 1.9
17g	6.7 ± 0.9	9.8 ± 0.5	36.2 ± 2.9
17h	1.9 ± 0.4	8.7 ± 0.9	37.9 ± 2.4
17i	3.8 ± 0.9	8.7 ± 1.1	24.6 ± 1.5
17j	2.3 ± 0.4	8.5 ± 0.4	26.4 ± 2.9
17k	1.9 ± 0.6	9.3 ± 1.0	42.5 ± 2.4
17l	2.3 ± 0.7	7.3 ± 0.6	28.9 ± 1.5
17m	3.4 ± 0.7	10.4 ± 0.7	25.5 ± 4.0

17n	2.2 ± 0.4	10.2 ± 1.1	39.9 ± 3.2
17o	3.0 ± 0.9	9.7 ± 1.3	39.4 ± 2.8
17p	2.0 ± 0.1	13.1 ± 1.2	26.0 ± 3.1
17q	2.6 ± 0.1	13.0 ± 0.6	43.0 ± 4.1
18a	1.9 ± 0.8	10.3 ± 0.7	37.6 ± 3.5
18b	1.6 ± 0.6	10.4 ± 0.5	40.3 ± 3.1
18c	2.7 ± 0.8	9.6 ± 1.3	26.3 ± 2.5
18d	2.8 ± 0.6	12.6 ± 1.0	44.0 ± 1.3
18e	3.1 ± 1.2	14.1 ± 0.6	49.0 ± 4.1
18f	2.6 ± 1.0	13.9 ± 1.1	47.4 ± 2.6
piperine (**14**)	3.4 ± 1.1	10.4 ± 0.6	17.9 ± 2.4
spirodiclofen	21.5 ± 1.7	69.3 ± 2.2	88.1 ± 1.6

[a]Values are the mean ± SD of three replicates.

The acaricidal activity of compounds **1a**, **1b**, **2a**, **2b**, **17a-q** and **18a-f** against the female adults of *Tetranychus cinnabarinus* was evaluated by slide-dipping method at a concentration of 1 mg/mL.[30,31] Spirodiclofen was used as a positive control at 1 mg/mL. As shown in Table 2, the mortality rates at 72 h of tested compounds were generally higher than those at 24 and 48 h. Xylose (**1a**), glucose (**1b**), 1,2,3,4-tetra-*O*-acetylxylose (**2a**), 1,2,3,4,6-penta-*O*-acetylglucose (**2b**), and piperine (**14**) nearly had no acaricidal activity against *T. cinnabarinus*; for example, the mortality rates (MRs) at 72 h of **1a**, **1b**, **2a**, and **2b** were all less than 5%. However, the glucose (xylose)-piperic acid conjugates (**18a-f**) and glucose (xylose)-piperic acid-like conjugates (**17a-q**) exhibited the potent acaricidal activity. The MRs at 72 h of all compounds were indicated in Table 2, the best candidates being those who were in the range of 32-49%. Among all derivatives, the acaricidal activity of 2,3,4-tri-*O*-acetyl-*β*-*D*-xylopyranosylcarbonyl derivatives **18d-f** was more potent than that of other derivatives; especially compounds **18e** and **18f** showed the most potent acaricidal activity. The MRs at 72 h of **18e** (49.0%)

and **18f** (47.4%) were improved more than 2-fold of that of **14**. It also showed that the 3,4-methylenedioxy of **18e** and **18f** was necessary for the activity (e.g., **18e** (49.0%) vs. **17q** (43.0%), **17n** (39.9%) and **17k** (42.5%); **18f** (47.4%) vs. **17o** (39.4%) and **17l** (28.9%)). Meanwhile, it suggested that introduction of the xylose moiety into piperic acid conjugates could give more potent compounds than those containing glucose moiety (e.g., **18d** vs. **18a**; **18e** vs. **18b**; **18f** vs. **18c**).

In summary, we have prepared a series of glucose (xylose)-piperic acid/piperic acid-like conjugates. Four single-crystal structures of **17b**, **17g**, **17h**, and **17n** were well confirmed by X-ray diffraction. Among all derivatives, compounds **18e** and **18f** exhibited the most promising insecticidal and acaricidal activities against *Mythimna separata* and *Tetranychus cinnabarinus*. It suggested that the 3,4-methylenedioxy group of glucose (xylose)-piperic acid conjugates was important for insecticidal and acaricidal activities, and introduction of the xylose moiety into piperic acid conjugates could give more potent compounds than those containing glucose one.

Acknowledgements

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Supplementary data

Supplementary data (spectral data, X-ray crystal structures, and the protocol used for insecticidal and acaricidal studies) associated with this article can be found, in the

online version.

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